Pediatric RESEARCH

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COMMENT

# Commentary on "The long-term effect of perinatal asphyxia on hippocampal volumes"

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Neonatal hypoxic ischemic encephalopathy (HIE), occurring in 1–6/1000 live births, is a leading cause of neurological impairment among children. The cognitive sequelae of HIE, previously thought to occur solely in the presence of cerebral palsy, have come to be recognized as a spectrum of functional neurobehavioral deficits that often occur in the absence of motor impairment.[1,2] Several decades of research using more comprehensive measures of cognition have demonstrated memory, language, executive function, and neuropsychological impairments among survivors of HIE.[3]

Alongside advances in our understanding of these functional impairments, sophisticated imaging techniques have been developed, enabling more detailed measures of the spectrum of hypoxic ischemic brain injury in neonates presenting with HIE. Diffusion weighted imaging, spectroscopy, brain morphometry, and volumetric analysis using manual and automated segmentation methods are being utilized to delineate regional brain changes previously undetected on qualitative standard neuroimaging. In one study linking structural and functional outcomes, Gadian et al. described five young patients with perinatal hypoxic ischemic brain injury who later showed significant impairments of episodic memory (memory for events), with relative preservation of semantic memory (memory for facts).[4] Notably, bilateral severe hippocampal atrophy was detected with quantitative MRI in all cases.[4] In these children, it appeared that the degree of hypoxia-ischemia was sufficient to damage the hippocampi, a "selectively" vulnerable brain region, without extensive injury to other brain regions vulnerable to more severe hypoxia-ischemia. Subsequent studies have shown that this pattern of memory deficit, called developmental amnesia, is characteristic of early-life hippocampal hypoxic ischemic injuries.[5] Given the challenges in recognizing episodic memory impairments clinically, these findings highlight the potential role of quantitative MRI in guiding development and education supports for children who experienced early-life hypoxia-ischemia.

In this issue, Annink et al. (citation) performed MRIs on 52 nine and ten-year-old survivors of neonatal HIE. Using automatic segmentation, they report smaller hippocampal volumes among children with a history of moderate neonatal HIE, with a trend toward smaller hippocampal volumes in mild HIE, compared to controls. The HIE group had lower IQ scores and poorer long-term episodic memory than controls, and the degree of HIE correlated negatively with IQ. Importantly, this paper demonstrates a significant positive association between hippocampal volumes and long-term *episodic* memory.

The interesting findings of Annink et al. prompt us to consider the impact of neonatal hypoxic ischemic brain injuries more broadly: (i) the spectrum of hippocampal-mediated cognitive outcomes, (ii) the array of regional brain structures that are vulnerable to hypoxic ischemic injury, and (iii) the larger framework of long-term implications of mild and moderate HIE.

Studies on episodic memory and its underlying neural mechanisms reveal surprising hippocampal involvement in functions that would ostensibly appear not to involve memory.[6] The retrieval of episodic memories mediated by the hippocampus has been found to play a role in imagining future scenarios,[7] problem solving[8,9], and displaying empathy.[10] Most recently, research in mice has provided further insight into the critical role the hippocampus plays not only in the storing and recall of fearful memories, but also in their attenuation and extinction, allowing for the development of adaptive responses to remote traumatic events.[11,12] The hippocampus' extensive contribution to functions that are integral to memory and emotion implicate its role in neurobehavioral disorders such as anxiety, post-traumatic stress disorder, and mood disorders among adults. Children who suffer early hippocampal injury have been found to have a unique neuropsychological profile with selective impairments.[5] Whether hippocampal impairment underlies the increased rates of neurobehavioral issues seen in childhood survivors of neonatal HIE warrants further attention.[13]

Beyond the hippocampus, advanced MR image processing techniques are revealing new patterns of brain injury relevant to cognition that are not readily visible on conventional MRI. The predominant patterns of hypoxic ischemic injury have been well characterized and correlated with outcomes in several MRI based studies, showing poor motor and cognitive outcomes for the basal ganglia-thalamus predominant pattern and latent cognitive and language deficits associated with watershed predominant parasagittal injury pattern.[14–16] Recent studies using diffusion tensor imaging have also revealed occult injury to the cerebellum, a structure intricately involved in learning and previously thought to be resistant to hypoxic damage.[17,18] Using deformation based morphometry of structural MRI in a cohort of infants with HIE studied at 6 months of age, Shapiro et al. identified volumetric changes in a network of areas involved in language processing in infancy that were found to be linked with language outcomes at 30 months.[19] Future directions also include investigating the neural networks connecting the hippocampus with other structures, such as the amygdala and prefrontal cortex and examining whether altered networks underlie the variability in cognitive

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outcomes following seemingly similar degrees of hypoxic ischemic brain injury.

This study also contributes to the mounting evidence for short and long-term implications of less severe forms of HIE.[20] The first prospective multicenter study designed to examine the outcomes of mild HIE recently published its short-term results, showing abnormal imaging, EEG or neurological exam, in approximately half of participants.[21] Moreover, a recent systematic review on the long-term neurodevelopmental outcomes of mild HIE demonstrated poor outcomes defined as death, motor, or developmental delay in approximately one quarter of infants.[22] Consequently, many centers now offer cooling to infants with mild neonatal encephalopathy.[23] Even among mild HIE infants who have undergone therapeutic hypothermia, studies show hypoxic ischemic injury in a significant number of cases. For example, Walsh et al. retrospectively analyzed neonatal MRI images among infants with HIE of varying levels of severity, all of whom had received therapeutic hypothermia and found that almost one quarter of infants with mild HIE had moderate-severe cerebral injury that was indistinguishable from those with moderate-severe encephalopathy.[24] These findings suggest the need for new methods of neuroprotection that address the full spectrum of HIE severity.

Given the greater availability of neonatal MRI and the clinical indication for imaging in neonatal encephalopathy,[25] a key question is when these changes in the hippocampus can be robustly detected. The present study delineates changes in the hippocampus that can now be probed in neonatal MR data. Early detection of these changes will be crucial to target interventions and rehabilitative services at preschool age that will maximize educational abilities, by reinforcing the use of compensatory mechanisms to support the impaired episodic memory at a time when children's semantic memories are increasing rapidly. During the school years, children with episodic memory impairment often have trouble acquiring new information, learning at a slower pace and requiring repeated exposure to the material.[26] The detection of hippocampal changes in childhood, as done by Annink et al., might enable specific educational strategies tailored to suit the cognitive needs of these children.

The findings of Annink et al. provide a valuable step forward in conferring more accurate prognoses when counseling families of survivors of moderate HIE, a group with a variable outcome that is traditionally difficult to predict. In a recent study aimed to address the needs of parents of children with neonatal brain injury, Williams et al. found that all of the parents interviewed expressed interest in understanding how their child's brain or medical condition impacts their behavior and learning.[27] The findings of Annink et al. highlight the important potential for intervention beyond the period of neonatal intensive care, including education, rehabilitation, and supporting the mental health of families. Looking ahead, as increasing numbers of children survive HIE, these newly recognized structural and functional changes will hopefully enable us to gain insight into targeted neuroprotective strategies that will ultimately promote better outcomes.

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